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REMARKS

The Rejection Under 35 U.S.C. § 103

The rejection of claims 12-18, 20-21, 38-41 and 42-43 under 35 U.S.C. § 103, as being obvious over Kendall (U.S. Patent No. 5,026,728) in view of Caughey (1983 article) or Gibson (1980 article) or McFarlane (U.S. Patent No. 4,455,298) is respectfully traversed.

Applicants maintain their position that the original data of record in the specification supplemented with further proof of unexpected advantages in the previously submitted Declaration of Dr. John Lawson show unexpected, advantageous properties representative of the full scope of the claimed subject matter and, thus, provide clear and convincing evidence of the nonobviousness of the claimed invention. The data as a whole establish that the combination of DMG and Perna provides a significant and unexpected advantageous result over what would have been expected from the prior art teachings pertaining to the use of either DMG or Perna alone. Applicants' disclosure and data show that the combination exhibits properties useful for treating human systematic lupus erythematosis (SLE), hereinafter "lupus" and/or providing a particular combination of immune response effects, neither of which could have been expected by combining the prior art taught effects of DMG and Perna administered alone. The prior art, when viewed as a whole in light of this evidence, does not support obviousness under 35 U.S.C. § 103.

The Examiner alleges that the data in the Lawson Declaration cannot be considered to show nonobviousness because the data was generated after the invention was made. This position is completely contrary to the established law and PTO practice. The law clearly allows for – and mandates consideration of – data generated after filing which shows the properties of compositions supported by the disclosure. This basic tenet goes at least as far back as Ex parte Ladd, 112 USPQ 337 (POBA 1955). In fact, it is the usual case that data

submitted under 37 C.F.R. § 1.132 to show nonobviousness is generated post-invention. The properties of a composition naturally flow from the composition. And the advantages shown for applicants' compositions in the Lawson Declaration directly relate to the advantages of the compositions particularly recited in the original disclosure, i.e., for treating lupus erythmatosus and modulating immune responses to inflammatory diseases; see, e.g., the first paragraph of the Summary of the Invention on page 3. The data in the Lawson Declaration merely provides further proof of this fact. Further, this proof is submitted in response to the Examiner's previous position that the amount of data in the specification was not sufficient. Thus, not only is the refusal to consider the data in the Lawson Declaration contrary to the law and PTO practice, it is particularly frustrating in that the very manner of data that was deemed necessary in the previous Office Action is now being refused consideration. Because the Lawson Declaration was improperly discounted, the arguments made in connection therewith are repeated below. Full weight and consideration should be given.

The Lawson declaration shows that, unexpectedly from the cited prior art, the combination of DMG and Perna is effective for treatment of nephritis in MRL lpr/lpr mice and, thus, reasonably expected to be effective against human lupus because this is the prevalent animal model used for modeling treatment of lupus in humans (see, e.g., pages 1-2 and the beginning of the Discussion section of the declaration). When they are administered together, DMG and Perna significantly amplified the down regulation of IgG-2a as compared to the DMG or Perna alone (see, e.g., Figures 7 and 10). Further, the combination of DMG and Perna significantly suppressed the development of glomerulonephritis and lymphadenopathy in MRL lpr mice (see, e.g., Tables 8-11). These results suggest that the combination of DMG and Perna ameliorates the lupus-like autoimmune disorders by modulating Thl, which in turn results in skewing positively of the immune response in

MRL/lpr mice. The DMG and Perna combination clearly suppressed the production of IgG-2a level in serum (see, e.g., Figure 6). It did not change that of IgGl (see, e.g., Figure 11) but increased the production of IgG3 in serum (see, e.g., Figures 11 and 12), thus, the total concentration of immunoglobulin essentially remained the same. DMG and Perna showed significant effects on lymphadenopathy. Average lymph nodes weight for mice treated with the highest concentration of DMG (200 mM) plus Perna was reduced to half compared to control mice. This reduction was also seen in other treatment groups with 100 mM DMG but not as significant as in 200 mM treated mice. Animals treated with different concentrations of Perna plus 150 mM DMG showed similar results (see Tables 10 and 11). Thus, Dr. Lawson concluded, it is shown that the immunomodulation resulting from the combination of DMG and Perna significantly reduces the progression of glomerulonephritis and pathological IgG-2a antibody levels and significantly reduced the pathological enlargement of the lymph nodes, these properties being shown in the prevalent mouse model being of high significance to treating SLE patients with glomerulonephritis. Such significant property of the DMG and Perna combination could not have been expected by one viewing the previous reports on uses of DMG and Perna.

The data from the instant specification bolsters the case for nonobviousness. It provides a side-by-side comparison of immune responses in the established prevalent animal model for human lupus. The data show that the combination of DMG/Perna provides an advantageous result, which is not merely the expected combined effect of DMG and Perna alone but an effect, which is **different in kind** than what would have been expected in the prior art. Particularly, the data showed:

- that il-10 cytokine production is **increased** with DMG alone and only slightly decreased, if any, with Perna alone,

- that the il-10 production is surprisingly **significantly decreased** by the combination of DMG and Perna according to the invention,
- that TNF-alpha levels are **decreased** with either of DMG or Perna alone but, surprisingly, **increased** by a combination of DMG and Perna,
- that the DMG/Perna combination, over either of DMG or Perna alone, reduces CD8 and CD19 lymphocytic markers,
- that the DMG/Perna combination, over either of DMG or Perna alone, reduces anti-dsDNA antibody levels and anti-ssDNA antibody levels.

The significance of these results (as discussed in the specification, Example 2; see page 11, first two full paragraphs) includes that they are indicative of a shift from a Th2 type response to a Th1 response for these cytokines. Such a shift is of high significance to the immune response generated, as discussed previously.

The claims are commensurate in scope with the unexpected results shown. They are significant and reasonably representative of the scope of the claimed subject matter; see, e.g., In re Kollman, 201 USPQ 193 (CCPA 1979). The use of the specific animal model is warranted by the fact that it is the model most prevalently used in the art for modeling the human lupus condition. As for the specific composition, the claims are also so limited, i.e., to a combination of DMG and Perna and to an enteral but not parenteral mode of administration. As to the dosages, the data from the specification is supplemented with that in Dr. Lawson's declaration wherein DMG and Perna are administered in varied concentrations and a new larger test and control group of the MRL/lpr mice are used. The data is reasonably representative of the advantage, particularly in light of the fact that the art gives no hint to such advantageous combination.

The showings here are reasonably representative of the entire claimed scope at least because: 1) MRL/lpr mice are the accepted model in the art for human lupus conditions, 2) the prior art gives no hint of anti-lupus activity for Perna, thus any such activity demonstrated by the combination of DMG and Perna could not have been expected – as further discussed below – and 3) the combined data of the specification and Dr. Lawson's declaration (which must be considered) shows such advantages in a significant number of tests.

Kendall '728 provides a broad generic teaching which includes lupus in a list of autoimmune diseases treatable using DMG. But the secondary references directed to the use of Perna provide no suggestion to use Perna for treating lupus or that Perna would effect the kind of immune response shown by applicants. The allegation in the Office Action that it is well-known that SLE is often treated with anti-inflammatories and, thus, it would obvious that Perna would be effective to treat SLE is unsupported on the record. There is no basis to suggest that it would be obvious to one of ordinary skill in the art to use any anti-inflammatory to treat SLE and there is no teaching at all from the secondary references that Perna might be one anti-inflammatory particularly suited to treating SLE. The only suggestion of such and the only suggestion that the combination of DMG and Perna would be particularly advantageous for treat SLE comes from improper hindsight application of applicants' own teachings. There is no expectation in the art that a combination of DMG and Perna would be useful for treating lupus and/or effecting the immune response as demonstrated by applicants on the record. Accordingly, the data reasonably establishing the activity of the combination of DMG and Perna for treating lupus and/or for effecting the shown immune response are, in fact, unexpected results.

As to the ultimate determination of obviousness, applicants do not disagree with the statement in the Office Action that a showing of unexpected results is but one factor to weigh

in the conclusion. Applicants' point was that such showing must in fact be considered and given fair weighting. That is, the evidence of nonobviousness cannot be ignored because it is believed a prima facie case of obviousness is established. Further, the evidence should be given considerable weight because it is a clear and convincing showing of an advantageous property of the combination which could not have been expected from the prior art teachings.

Applicants have shown that their novel combination provides significant and advantageous properties that would not have been expected by one of ordinary skill in the art for such combination. Accordingly, applicants have provided an advance in the art which is deserving of patent protection. That the prior art might have *prima facie* suggested the two components could be combined to possibly provide an anti-inflammatory property does not lessen applicants' contribution of actually combining them, in the particular manner as claimed, and discovering the new and unexpected properties thereof in treating SLE and effecting the immune response. As established by In re Chupp, 2 USPQ 2d 1437 (Fed. Cir. 1987), to prove nonobviousness of a composition based on a showing of unexpected properties, the composition need not excel over the prior art in all common properties. A showing of superiority in only one property can be enough to prove nonobviousness.

Applicants remain of the position that Belkowski teaches away from the claimed invention and must be given its due weight. Applicants arguments on this have been set forth previously and are incorporated by reference here.

For all of these reasons at least, the rejection under 35 U.S.C. § 103 based on the combination of the Kendall '728 reference with Caughey or Gibson or McFarlane '298 should be withdrawn.

The Rejection Under 35 U.S.C. § 112

The rejection of claims 12-18, 20-21, 38-41 and 42-43 under 35 U.S.C. § 112, first paragraph, for lack of written description, is respectfully traversed.

The withdrawal of the rejection as to the "not sterilized" term is respectfully acknowledged.

Applicants agree with the characterization in the Office Action that by the recitation of the "enteral but not parenteral administration" form they are claiming the portion of the enteral administration forms which does not overlap with parenteral administration forms. This subgenus, however, is not new matter. The specification clearly supports that enteral forms are optional and parenteral forms are optional. Thus, it contemplates forms which are: 1) enteral, 2) not enteral, 3) parenteral and 4) not parenteral. From such disclosure, one of ordinary skill in the art would immediately envisage support in the specification for the subgenus combining options 1) and 4). It is not necessary for this to be literally recited in the specification in order to be supported. Further support for claim term is evidenced by the facts that:

- one of ordinary skill in the art would interpret the term "enteral" as being distinguished from "parenteral,"
- it is known that, in practical terms, enteral and parenteral administration forms have very different requirements, e.g., parenteral forms must be sterile,
- enteral forms need not be sterile,
- the specification describes forms for enteral administration which are not suitable for parenteral administration (e.g., they are not sterilized) as one option, and

- the specification actually provides Examples where the administration form is suitable for enteral administration but not for parenteral administration.

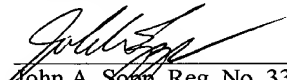
The opinions of Drs. Kendall and Lawson in their declarations on this point are not necessary but further support applicants' position. It is noted that Dr. Lawson stated his own independent opinion, not an opinion of Dr. Kendall's opinion, as appears to be alleged in the Office Action. Further, the position in the Office Action appears to be that Dr. Kendall's opinion is not convincing because he is not an expert and Dr. Lawson's opinion is not convincing because he is an expert. Clarification of this apparent position is requested since it is not understood.

For the above reasons, it is urged that the 35 U.S.C. § 112, first paragraph, rejection should be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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